

Serial No. 10/506,952  
Page 4

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## REMARKS

### Amendment

Prior to the above amendment, Claims 1-9 were pending in the application and have been rejected.

The subject matter of claim 2 has been incorporated into claim 1, and Claim 2 has been cancelled without prejudice in order to expedite prosecution. It is respectfully submitted that this amendment does not introduce new matter to the present application.

Claims 3 and 4 have been amended to correct dependency.

Claims 1 and 3-9 are currently pending.

### Claim Rejections – 35 USC §102

Claims 1, 5-6, and 8-9 have been rejected under 35 U.S.C. 102(b) as being anticipated by Hutchinson (US 5,889,110).

It is noted that the above rejection was not applied to claim 2. In order to expedite prosecution, the subject matter of claim 2 has been incorporated into claim 1 (the sole pending independent claim). It is respectfully submitted that this rejection is now moot.

### Claim Rejections – 35 USC §103

Claims 1-9 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Hutchinson (US 5,889,110) in view of Bhagwatwar et al (US 2003/0049320) and Yeh et al (US 5,869,103, cited by International Authority in related PCT Search Report).

The present invention as set forth in the amended claims provides a method for the preparation of nano- or microparticles, wherein an active substance is embedded in a polymer matrix by precipitating the active substance in a composition containing the

Serial No. 10/506,952

Page 5

polymer, and subsequently solidifying the polymer. This process is carried out by first combining a solution of an active substance dissolved in a smaller amount of a first solvent L1 with a solution of a polymer in a larger amount of a second organic solvent L2. The solvent L2 dissolves the polymer but is a non-solvent for the active substance. Upon mixing of these compositions, the active substance is precipitated and suspended in a solution comprising the polymer. After this step, the suspension is mixed with an aqueous surfactant solution and the polymer is solidified to obtain a suspension of nano- or microparticles that contain an active substance.

Thus, instead of adding the active substance in a solid state to the polymer solution, the active substance particles are formed in situ. Note that this precipitation takes place in a solution wherein the polymer is still dissolved in an organic solvent. Only after precipitation of the active substance, the polymer is solidified to form the suspension of nano- or microparticles.

The present claims provide a unique and simple in situ precipitation and encapsulation, wherein the active substance is precipitated by creating a solution containing a mixture of solvents in the presence of a solvated polymer in a manner that will lead to precipitation of the active substance, followed by solidification of the polymer to provide a unique particulate, solid form. The present method does not require sophisticated freeze drying techniques, and provides a system wherein a unique interaction of components is achieved through the order of precipitation of the active substance in the presence of the polymer. By the sequential precipitation of the active substance by selection of solvents, followed by solidification of the polymer, formation of nano- or microparticles containing an active substance embedded in a polymer matrix is carried out by a convenient and economical process. Moreover, by emulsifying a polymer solution containing an active substance in a finely dispersed solid form in the presently claimed manner, negative effects of shear forces on the active substance can be avoided (cf. page 3, lines 15-20 of the present application).

Hutchinson does not teach the step of precipitation of the active substance prior to solidification of the polymer to form the suspension of nano- or microparticles.

Serial No. 10/506,952

Page 6

Hutchinson discloses salts composed of a cation derived from a peptide containing at least one basic group and an anion derived from a carboxy-terminated polyester, processes for the manufacture of such salts, and the use of such salts in the manufacture of extended release pharmaceutical compositions (i.e. microparticles). See the Abstract. The process of making such microparticles is detailed, for example, in claim 16, which states:

16. Microparticles comprising a composition consisting essentially of a salt formed from a cation derived from a peptide containing one or more basic groups and an anion derived from a carboxy-terminated polyester, which composition has been prepared from at least an approximately stoichiometric equivalent of said polyester carboxylic acid end groups relative to said basic peptide groups, obtainable by a process comprising

i) dissolving the basic peptide and carboxy-terminated polyester in a first solvent in which both the peptide and the polyester are soluble to form a first solution;

ii) freezing said first solution at high speed to form a frozen mixture;

iii) freeze-drying the frozen mixture to remove said first solvent, forming a freeze-dried product;

iv) dispersing the freeze-dried product into a second solvent which is a solvent for the polyester and a non-solvent for the peptide to form a second solution containing said peptide/polyester salt; and

v) removing said second solvent from said second solution by a procedure selected from the group consisting of spray-drying, spray-congealing, evaporation and phase separation coacervation to form a solid product which is in the form of microparticles, or from which said microparticles are thereafter formed.

(emphasis provided)

Note that the first solvent and the second solvent of Hutchinson are never together in the same solution. The first solvent is removed in step iii) before the second solvent is introduced in step iv). The Office Action states in the passage bridging from page 3 to page 4 that a precipitation of an active substance is carried out in the prior art by using a

Serial No. 10/506,952

Page 7

non-solvent for this substance. However, in the invention described in Hutchinson, the non-solvent is added to a solid form of the active substance under consideration. See claim 16, step iv). Because the active substance in the claimed process is already in solid form, no precipitation of the active substance can occur at this step of the process.

The gap between Hutchinson and the present invention is not bridged by Bhagwatwar et al or Yeh et al.

Bhagwatwar is cited for its disclosure of forming microparticles comprising the elected species of active substance goserelin acetate and polymer poly-DL-lactide-co-glycolide with any suitable solvent. Bhagwatwar does not contemplate precipitation of the drug in the polymer solution prior to solidifying the polymer, as is required in the present claims. Bhagwatwar does not add anything to the disclosure of Hutchinson relative obviousness of the present claims.

Yeh is cited for its disclosure of formation of nano/microparticles comprising active substances and poly-DL-lactide-co-glycolide. . However, as in Bhagwatwar, the active agent of Yeh is provided in a solution, emulsion or suspension that is mixed with the polymer solution. A third solvent is mixed with this solution to precipitate the polymer and form the microspheres. See column 4, lines 35-50. Thus, there is no teaching or suggestion of precipitation of the active agent in the polymer solution prior to solidifying the polymer, as is required in the present claims.

Neither of these references are concerned with any precipitation of active substances, let alone in the specific manner as it is claimed in the present claims. Reconsideration and withdrawal of the outstanding rejection is therefore respectfully requested.

#### **Claim Rejections – 35 USC § 112 2<sup>nd</sup>**

Claims 1-9 have been rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention.

Serial No. 10/506,952  
Page 8

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JUL 19 2007

It is respectfully submitted that the claim amendments above address the concerns raised in the Office Action relative to the aspect of "effecting precipitation" as recited in claim 1.

The Office Action further states that it is unclear what the agents and amounts are contemplated as L1 and L2. The present invention is the first to disclose the principle of precipitating an active substance in a solution of a polymer, and then solidifying the polymer to obtain a suspension of nano- or microparticles by manipulation of solvents. It is respectfully submitted that the identity and amounts of the solvents to be used are clear on the face of the claims, namely that L1 is a solvent that can dissolve the active substance, and L2 is a solvent that can dissolve the polymer but not the active substance. Armed with this knowledge, the skilled artisan is fully capable of identifying appropriate solvents based on any given active substance and polymer by routine tests or reference to solubility parameters. Furthermore, the present specification provides extensive teaching in particular for choice of solvents relative to the active substance to be encapsulated beginning at page 8, line 27. A lengthy list of polymers is provided at page 6.

With respect to amounts, the skilled artisan is fully capable of identifying such parameters because they are armed with the knowledge provided by the present specification. For example, the specification teaches how to effect the precipitation by manipulation of solvents, particularly beginning at page 7, line 7.

It is respectfully submitted that the plain meaning of the language of the claims is clear on its face to the skilled artisan, particularly in view of the extensive teaching provided by the present specification.

### **Objection to the Specification**

The use of trademarks as they appear in the present specification has been objected to. It is respectfully submitted that the trademark usage is proper in the context of the specification. The objective of the rules relative to trademark usage in the US Patent Office is to assure that the proprietary nature of trademarks are respected. In the present

Serial No. 10/506,952

Page 9

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JUL 19 2007

application, all marks are clearly indicated to be trademarks by use of the <sup>TM</sup> symbol, and additionally the generic description for each product is associated with the mark.

### Conclusion

In view of the above amendments and remarks, it is respectfully submitted that the foregoing is fully responsive to the outstanding Office Action. Examination of all claims together, and early favorable consideration and passage of the above application to issue is earnestly solicited. In the event that a phone conference between the Examiner and the Applicant's undersigned attorney would help resolve any issues in the application, the Examiner is invited to contact said attorney at (651) 275-9811.

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Respectfully Submitted,

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